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A PILOT STUDY OF TUMOR LYSATE-PULSED DENDRITIC CELL VACCINE IN PEDIATRIC HIGH-RISK SOLID TUMOR PATIENTS FOLLOWING HCT: PRELIMINARY RESULTS

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Pediatric pts with metastatic or recurrent solid tumors often relapse even when remissions are consolidated with high dose chemotherapy and autologous hematopoietic cell transplant (HCT). We previously showed dendritic cell (DC) based tumor vaccines to be safe and produce anti-tumor responses in children with refractory solid tumors. Experimental evidence indicates that the period of lymphopenia that occurs after HCT may be an opportune time to improve the immune response to self tumor. Furthermore, a DC based tumor vaccine may be most effective when residual disease burden is minimal, as in the period immediately after HCT. We are testing this hypothesis in an ongoing clinical trial of tumor-lysate pulsed DC vaccination shortly after HCT for high-risk pediatric solid tumor pts. Ten pts (median 15y, range 2–21y) have been treated to date. All patients had metastatic tumors (high grade sarcoma-6, neuroblastoma-3, Wilms-1), 6 pts had recurrent disease. Autologous tumor collected at time of diagnostic or therapeutic surgery and mononuclear cells collected at stem cell harvest for HCT were cryopreserved for later vaccine generation. Vaccines were generated by pulsing tumor lysate and keyhole limpet hemocyanin (KLH) as an immunoadjuvant onto immature DC for 4h followed by addition of a maturation cocktail of IL6, IL1β, PGE2, and TNFα for 18h. Patients in partial remission or better underwent high-dose alkylator based autologous HCT. Intradermal DC vaccines given every two weeks for a total of 3 vaccines began at a median of 20d, (range 14–36d), soon after the absolute lymphocyte count reached 200/μl. There have been no vaccine associated toxicities or development of autoimmune disease. Prior to HCT and 2 weeks after the 3rd vaccine, immune testing, including antigen specific T-cell detection by IFNγ elispot assay, was performed. A 3-fold increase in the numbers of IFNγ-secreting T cells was considered a positive result. Positive responses were observed to KLH in 9/10 pts (median increase 20×, range 0.9–351×) and to tumor lysate in 6/10 pts (median increase 6×, range 0.1–21×). Median follow-up is 12 months. 2/6 pts with response to tumor have relapsed, 3/4 pts without response have relapsed. Immunologic and clinical responses are shown in the table. These preliminary results indicate that a DC-based vaccination strategy initiated during the early post-HCT lymphopenic period can generate strong anti-KLH and tumor lysate responses.

Immunologic and Clinical Responses

Patient	Age (years)	Pre-HCT status	KLH response	Tumor lysate response	Status @ 2m post-HCT	PFS (months)
Neuroblastoma	3	PR (MIBG avid abdominal mass)	+	++	CR	10+
Recurrent Neuroblastoma	3	CR	+++	++	CR	12
Recurrent Neuroblastoma	17	PR (MIBG avid mediastinal mass)	++	-	SD	3
Synovial sarcoma	17	PR (lung mets)	-	+++	CR	7+
Malignant peripheral nerve sheath tumor	10	CR	+++	+++	CR	12+
Recurrent Osteosarcoma	19	PR (lung mets)	+++	+	SD	3
Recurrent Ewing's sarcoma	17	PR (pelvic mass)	+++	-	SD	3.5
Rhabdoid tumor of the abdomen	2	CR	+++	-	CR	3
Recurrent Chondroblastic sarcoma	21	PR (lung and spinal mets)	+	+	SD	15+
Recurrent Wilm's tumor	13	PR (lung mets)	+	-	CR	7+

If <3× baseline, -. If >3× baseline, strength of response based on elispot number: KLH <500 +, 500-1000 ++, >1000 +++; tumor lysate <100 +, 100-200 ++, >200 +++.

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TREATMENT OF HIGH-RISK NEUROBLASTOMA WITH ADOPTIVELY TRANSFERRED T LYMPHOCYTES GENETICALLY ENGINEERED TO RECOGNIZE GD2

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Background: Adoptive transfer of tumor directed T cells may offer an alternative therapy for patients with advance stage solid tumors as they can expand *in vivo*, actively migrate through tissue planes, and use direct and indirect cytotoxic mechanisms to kill tumor cells. Two major limitations to clinical efficacy are the ability of many tumors to downregulate MHC expression and decrease susceptibility to antigen-specific T cell killing, and the lack of co-stimulatory molecules on tumor cells leading to incomplete T cell activation and poor survival. We attempted to overcome these limitations by generating an MHC-independent chimeric antigen receptor (CAR) targeting GD2, a tumor antigen expressed on almost neuroblastoma cells. We transduced activated T cells (ATC), and Epstein Barr virus-specific cytotoxic T lymphocytes (EBV-CTL) with a distinguishable GD2-CAR and infused them into patients with high-risk neuroblastoma. We compared the survival of EBV-CTL to ATC expressing the GD2-CAR and anticipated superior persistence of GD2 EBV-CTL due to *in vivo* co-stimulation received following engagement of their ***native*** antigen receptor by chronically expressed EBV antigens in seropositive individuals.

Study Design: The primary objective of this Phase I trial was to determine safety of escalating doses of GD2-ATC and GD2-CTL in high-risk neuroblastoma patients. A secondary objective was to compare the *in vivo* survival of GD2-ATC versus GD2-CTL.

Results: Fourteen patients with high-risk neuroblastoma received autologous ATC and EBV-CTL transduced with GD2 CARs. No dose limiting toxicities were identified. Of 12 currently evaluable patients, there was a >10-fold higher mean area under the curve (number x duration in weeks) of GD2-CTL than GD2-ATC in peripheral blood. 3 subjects had no evidence of disease at the time of infusion: one remains disease free >17 months post infusion; 2 are alive with disease at 13 and 34 months. Of the 9 with relapsed/resistant disease, 3 had stable disease for 10 to 16 months post-infusion, 2 developed tumor inflammation and necrosis, 1 had clearance of marrow disease at 6 weeks, and 1 has a complete response sustained for >24 months.

Conclusion: Treatment of high-risk neuroblastoma with adoptively transferred T cells expressing GD2 CARs appears safe and can be associated with anti-tumor activity. CAR-CTL may have a survival advantage over CAR-ATC due to the co-stimulation received during native receptor engagement by viral antigens.